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EXAMINER	
PAGONAKIS, ANNA	

ART UNIT	PAPER NUMBER
4173	

MAIL DATE	DELIVERY MODE
11/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,175	OSTROFF ET AL.	
	Examiner	Art Unit	
	Anna Pagonakis	4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *10-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9; 17-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group I, claims 1-9, 17-18 and specie election of trastuzumab as the antibody field on 09/26/2007 is acknowledged. Because applicant did not distinctly and specifically point out supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-9, 17-18 are presently under examination and are the subject of this Office Action.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The use of the trademark HERCEPTIN®, RITUXAN®, ERBITUX® (page 22 of specification) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 17, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the treatment of mammary carcinoma (specification page 38), the specification does not reasonably provide enablement for the treatment of other tumor types. The specification does not enable any person skilled in the art to which it pertains, or with which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention

2) the breadth of the claims

3) the predictability or unpredictability of the art

4) the amount of direction or guidance presented

5) the presence or absence of working examples

6) the quantity of experimentation necessary

7) the state of the prior art

8) the relative skill of those skilled in the art

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently claimed invention is directed to a method of suppressing or eliminating tumor cells, by administering a therapeutically effective amount of insoluble beta whole glucan particles and an antitumor antibody.

In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the treatment of any tumor type could be effectively achieved by the administration of insoluble beta whole glucan particles and an antitumor antibody.

As set in In re Marzocchi et al., 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added).

Here, the objective truth that any tumor type may be treated with a therapeutically effective amount of insoluble beta whole glucan particles and an antitumor antibody is doubted because, while the state of the art of cancer treatment is well developed with regard to the treatment of specific cancer types with specific chemotherapeutic regimes (see Cecil's Textbook of Medicine, pages 1060-1074), the state of the art with regard to treating all tumors using a single agent is grossly underdeveloped.

In this regard, Cecil's Textbook of Medicine (2000) is cited. In particular, there is no known anticancer agent or combination of anticancer agents that is effective against treating all cancer types, nor is there any known anticancer agent or combination of agents that is effective against inhibiting the growth of any type of cancer cell. The Cecil reference clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective at treating cancer or inhibiting the growth of cancer cells for each and ever type of cancer (see Table 198-5 at page 1065; Tables 198-6 and 198-7 at pages 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

Given that there was not known any specific agent or combination of agents effective to treat all known types of cancer, one of ordinary skill in the art would not accept on its fact Applicant's statement that such an objective could be achieved in any type of tumor using the presently claimed insoluble beta whole glucan particles and an antitumor antibody without enabling a set of species representative of the full scope of cancers known in the art. The artisan would have required sufficient direction as to how, at minimum, a representative set of species of cancer could be effectively treated with insoluble beta whole glucan particles and an antitumor antibody and, further, how the artisan could have reasonably extrapolated such results to the larger and highly varied genus of tumors in general without requiring undue experimentation to determine what types of tumors would actually show sensitivity to the presently claimed insoluble beta whole glucan particles and an antitumor antibody, such that the artisan would have been imbued with at least a reasonable expectation of success in treating the tumor. Such success would not have been reasonable expected for all tumor types would not have been considered representative or suggestive of the same efficacy in the treatment of all known types

of tumor in the absence of any evidence or reasoning to do so. Additionally, since the skilled artisan would have expected the interaction of a particular agent in the treatment of a particular disease state to be very specific and highly unpredictable absent a clear understanding of structural and biochemical basis for the use of each agent, one of skill in the art would have no other recourse but undue experimentation to undertake extensive testing to determine which other tumor types would be amenable to treating using a therapeutically effective amount of insoluble beta whole glucan particles and an antitumor antibody.

It is in this regard that Applicant is directed to the MPEP at 2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern in whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

A conclusion of la ck of enablement must take into consideration the unpredictability in the art at the time of invention and the direction or guidance provided by Applicant. The amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification needs more detail and guidance as to how to use the invention in

order to be enabling. Please reference In re Fisher, 417 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and Chiron Corp v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

The enablement of the working examples provided by the specification is not disputed. However, they are not representative of the breadth of the presently claimed subject matter. Applicant's claims broadly claim the use of a therapeutically effective amount of insoluble beta whole glucan particles and an antitumor antibody for *any tumor*. The fact that Applicant has exemplified use of this compound in mammary carcinoma cells does not address the high degree of variability in the art in terms of the pathophysiological differences among tumor types and their reactivity to different anticancer compounds. Applicant has also failed to provide any evidence, or describe any protocol, that addresses this variability in the art such that one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success in treating any tumor with the claimed compound based on the direction provided in the present specification. While the lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the Wands factors as a howle.

In light of such, it is clear that one of ordinary skill in the art would be faced with the impermissible burden of undue experimentation in order to execute the entire scope of the subject matter presently claimed. The basis of the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and

chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction of Applicant would be *undue*. Please reference In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added) Given the high degree of unpredictability noted and recognized in the art with regard to the treatment of tumors, the state of art clearly precludes the general exploitation of the results seen in two tumor types to the larger and much more highly varied genus of tumors as a whole. In the absence of any direction or guidance presented by Applicant as to how such a therapeutic objective could be achieved without necessitating an undue level of experimentation, the present disclosure is viewed as lacking an enabling disclosure of the *entire scope* of the presently claimed subject matter.

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several year of experience in the art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 and 17-18 are rejected under 35 U.S.C. 112, second paragraph, because the claims contain language, an "effective amount" which is vague and indefinite and does not

clearly specify what is meant by the "effective amount" as being effective for suppressing or eliminating.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 is drawn to administration of an antibody produced via a cancer vaccine. The term "cancer vaccine" encompasses a plethora of disorders. The specification does not define not discuss a "vaccine."

The term "vaccine" encompasses the ability of a specific antigen to induce protective immunity to cancer. The specification does not provide evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing cancer. Without this demonstration, the skilled artisan would not be able to reasonably predict if protective immunity has been induced. The specification has also failed to enable the use of the claimed vaccine in treating all types of cancer.

Bystryn *(Cancer and Metastasis Reviews, 9:81-18)* teaches that it is difficult to induce the rejection of already established tumors with vaccines (page 83). Bystryn teaches that the ideal cancer vaccine should be safe, effective against a broad range of tumors of the same histological type, sufficiently potent to require only a few immunizations, simple to manufacture in a reproducible manner, and stable for a prolonged period of time. Bystryn teaches that no such

vaccine is available (page 83). Bystryn teaches that the most basic requirement for a cancer vaccine is that it contains tumor antigens that can stimulate a strong and clinically effective anti-tumor immune response in humans (page 83). Bystryn teaches that little is known about the identity of such antigens (page 83). Bystryn teaches that most tumor antigens have been defined with monoclonal antibodies that are raised by immunizing animals with human tumor cells, however, the functional effect of the immune responses induced by these antigens is still not known (page 83). Bystryn teaches that for vaccine immunotherapy to be effective, the immune responses induced must be directed to the antigens expressed by the tumor being treated and unfortunately, the pattern of tumor antigens expressed by cancers of the same histological type in different individuals is variable (page 84). Bystryn teaches that there is variation in the pattern of tumor antigens expressed by different tumor nodules in the same individual and by different tumor cells in the same nodule (page 84). Bystryn teaches that it is unlikely that a single tumor antigen will be effective against a broad range of tumors of the same histological type (page 84). Gura *(Science 278:1041-1042, 1997)* teaches that researchers face the problem of shifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (see first paragraph of page 1041). Gura teach that appropriate animal models are necessary for the development of cancer drugs or vaccines. Gura teach that animal models are not affected in the same manner as humans in regard to cancer tumors and associated treatments (page 1041). Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative

skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

It is clear based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed cancer vaccine would function as contemplated in the specification, i.e. broad treatment of cancer. The specification also does not present sufficient working examples, which would provide guidance and significant preponderance of predictability to one skilled in the art to use the claimed cancer vaccine in therapeutically effective amounts with a reasonable expectation of success. There is limited evidence provided in the instant specification, which would allow one of skill in the art to predict that the claimed vaccines would confer protective immunity or generate an immune response in any and all cancers with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice (i.e. make and use) the invention as is broadly claimed.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification as filed does not provide sufficient guidance for the skilled artisan to predict what is a "synergistic antitumor effect." The skilled artisan prior to practicing the claimed invention must empirically determine these parameters.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jamas et al. (US Patent 5,532,223, A8 of IDS) in view of Leyland-Jones (The Lancet, Oncology Vol. 3 March 2002).

Jamas et al. discloses that zymosan, a crude insoluble yeast was shown to inhibit tumor development (column 1, lines 23-30). Subsequent studies identified the active components of the yeast cell wall as a pure polysaccharide, specifically beta glucan (column 1, lines 34-36). Furthermore, Jamas states that repetition of biological assays with beta glucan indicated that most of the above functional activities identified with zymosan were retained by the purified beta glucan preparation (column 1, lines 36-39).

Leyland-Jones teaches that trastuzumab is the first clinically available oncogene-targeted therapeutic agent for treatment of solid tumors (see abstract). The author further states that the possibility of introducing this agent into the adjuvant setting and the introduction of new combinations, doses and schedules remain exciting options (discussion, last paragraph). Additionally, the author discloses that trastuzumab provides a model of integration of new gene-targeted therapies (discussion, last paragraph).

One of ordinary skill in the art would be motivated to combine the above teachings and as combined would teach the invention as claimed. One of ordinary skill in the art would have been motivated by Jamas et al. and Leyland-Jones because both are directed to the treatment of tumors. See In Re Kerkhoven 205 USPQ 1069. The idea of combining the teachings of Jamas et al. and Leyland-Jones flows logically from having been individually taught by the prior art.

Additionally, one of ordinary skill in the art the administration and specific source of the compound (such as in the same formulation, different formulations, same route, different routes, orally, simultaneously and sequentially) is well within the knowledge of the skilled artisan to determine how and what formulation combination and mode of administering will be appropriate for the patient, which will depend on the type of tumor.

Double Patenting – Non-provisional

Claims 1-9, 17-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 15 of U.S. Patent Application No. 10/526,185

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the patented claims and those of the present application are considered to be patentably distinct from each other. The reasons are as follows:

Both sets of claims refer to suppressing or eliminating tumor cells by use of a glucan and an anti-tumor antibody – copending application claim 1.

Both applications recite using the same method of treatment. See current application claim 1 and copending application claim 1.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Pagonakis whose telephone number is 571-270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin H Marschel/
Supervisory Patent Examiner, Art Unit 1614